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LOCAL CEREBRAL BLOOD FLOW UTILIZING XENON-133

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Research was conducted according to the principles enunciated in the "Guide for Laboratory Animal Facilities and Care," prepared by the National Academy of Sciences - National Research Council.

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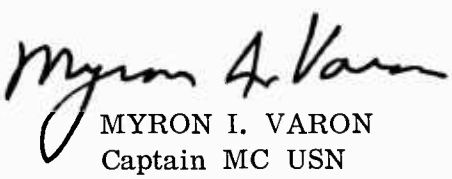

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ABSTRACT

An experimental method for determining local cerebral blood flow (CBF_l) within the area of supply of a major cerebral artery is described, using xenon-133. Utilizing anatomic-radiologic correlates, the territories of the anterior and middle cerebral arteries were defined in the rhesus monkey. Highly focused collimation was used so that isoresponse patterns allowed detection of activity from each territory separately. Compton scatter contributed only 10 percent to the total activity seen. CBF_l values were consistently and significantly higher in the anterior than in the middle cerebral distribution. The significance of these findings is discussed.

I. INTRODUCTION

Measurement of regional cerebral blood flow (CBF_r) utilizing gamma-emitting radionuclides is finding widespread clinical and experimental use. Abnormalities in CBF_r have been noted in a wide variety of pathologic conditions, and such information has been of definite prognostic value in selected instances.[1,3,4,6,8] Recordings are usually made by probes arranged to monitor the lateral radioactive emissions from the frontal, temporal, parietal and occipital lobes (Figure 1). This arrangement of probes will detect emissions from areas supplied by both the medially placed anterior and posterior cerebral arteries and the more laterally placed middle cerebral artery. Because of this overlap, a "regional" orientation of probes is unsuitable when one wishes to measure the flow within an area exclusively supplied by one of these major arteries.

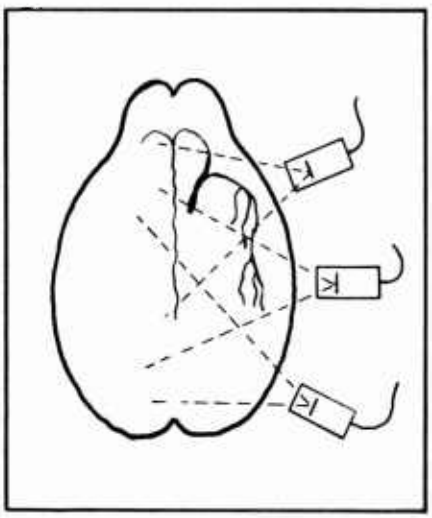

Figure 1. Vertex view. Probes arranged for conventional regional cerebral blood flow study will detect activity from both medial and lateral cerebral structures without distinguishing the arterial supply.

The purpose of this paper is to describe a method developed in rhesus monkeys to determine the cerebral blood flow in an area supplied primarily by either the anterior or middle cerebral arteries. In contrast to CBF_r this measurement may be referred to as "local" cerebral blood flow (CBF_l) and denotes the flow in brain tissue subserved by one of the three major cerebral arteries. Hopefully, this method will allow correlation of CBF_l values with angiographically demonstrable pathology in the larger cerebral arteries distal to the circle of Willis.

II. ANATOMIC CONSIDERATIONS

Rhesus monkeys (Macaca mulatta) were found to be the most appropriate experimental subjects for these initial studies. The cerebral circulation in the rhesus monkey is grossly similar to that in the human, except for the presence of a common pericallosal artery formed by the union of both anterior cerebral arteries.[2,13] This artery ascends in the midline maintaining a position just inferior to the free edge of the falx and gives branches to the medial aspects of both frontal and parietal lobes. The parenchyma supplied by the common pericallosal artery and its branches includes the corpus callosum and the cingulate and superior frontal gyri, as well as the medial aspects of the parietal lobes. In the coronal plane, it has a U-shaped configuration (Figure 2). On the other hand, the distribution of the middle cerebral artery, its lenticulostriate and candelabra branches, more closely approximates that seen in man.

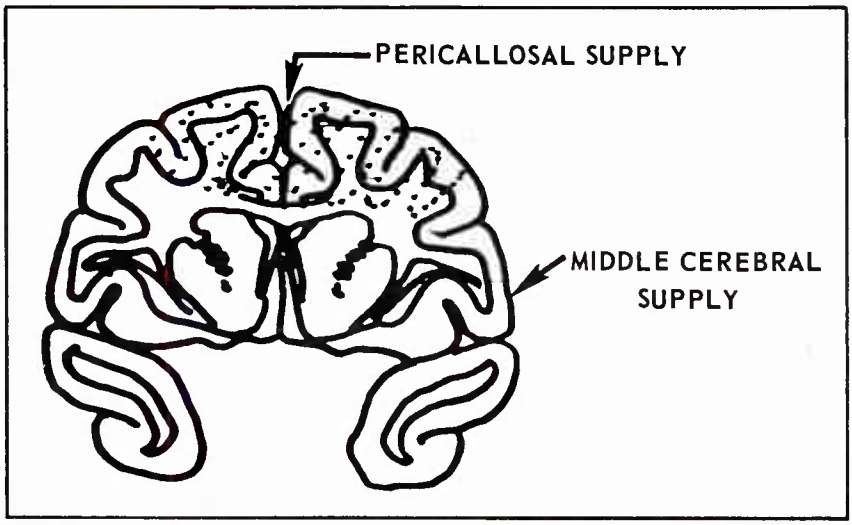

Figure 2. Coronal section of rhesus monkey brain illustrating the territory supplied by the common pericallosal artery (stippled) and middle cerebral artery (adapted from Coceani and Gloor[2])

III. METHODS

Sixteen rhesus monkeys weighing approximately 6 - 8 kg were tranquilized with intramuscular Sernylan* (phencyclidine hydrochloride) and anesthetized with intravenous Nembutal† (sodium pentobarbital). Endotracheal intubation was done, and the common carotid artery was exposed. A 20-gauge Teflon catheter was temporarily inserted into the common carotid artery for angiographic studies. A PE 190 catheter was inserted transfemorally into the abdominal aorta and connected via a Statham transducer to a cathode-ray oscilloscope (Electronics for Medicine, White Plains, New York) for continuous monitoring of mean blood pressure and intermittent sampling of arterial blood gases.

* Bioceutic Laboratories, St. Joseph, Missouri
† Abbott Laboratories, North Chicago, Illinois

Radiologic techniques. The position of the head was standardized for angiographic studies. Transorbital views (0^{o} angulation) were used to demonstrate the horizontal portions of the anterior and middle cerebral arteries, while lateral views were used for the internal carotid, pericallosal and middle cerebral arteries. Patency of both anterior cerebral arteries was confirmed by either bilateral carotid angiography or cross-filling after carotid compression. Following angiography, both CBF_l and CBF_r studies were performed, as described below.

Cerebral blood flow measurement. Cerebral blood flow measurements were made after advancing the catheter into the internal carotid artery. Xenon-133, 0.1-0.2 mCi, was rapidly injected, and washout was measured using a sodium iodide, thallium-activated (NaITl) crystal, 1 inch in diameter and 2 inches long. The crystal was shielded by a 7.6-cm, 19-hole, lead-focusing collimator with ultimate resolution of approximately 1 cm at the isotopic focal point. The tissue "viewed" by this crystal-collimator combination can be represented by a cylindrical core extending from the surface of the collimator to 14 cm in depth. This was verified experimentally by phantom (Figure 3), isoresponse, and line spread function studies (Figure 4).

The mock phantom was a Lucite-rice model constructed to represent the rhesus monkey skull, and measured 4.0 by 5.5 cm. Utilizing this model (Figure 3), studies were undertaken to ascertain the contribution of Compton scatter to the total activity recorded on the washout curves. A linear source, containing ^{197}Hg to simulate the emission of ^{133}Xe, was placed at the region of the sylvian fissure. This source yielded a count rate of approximately 10,000 counts per minute (cpm). An equivalent source was placed in the region of the pericallosal artery, and its contribution to the

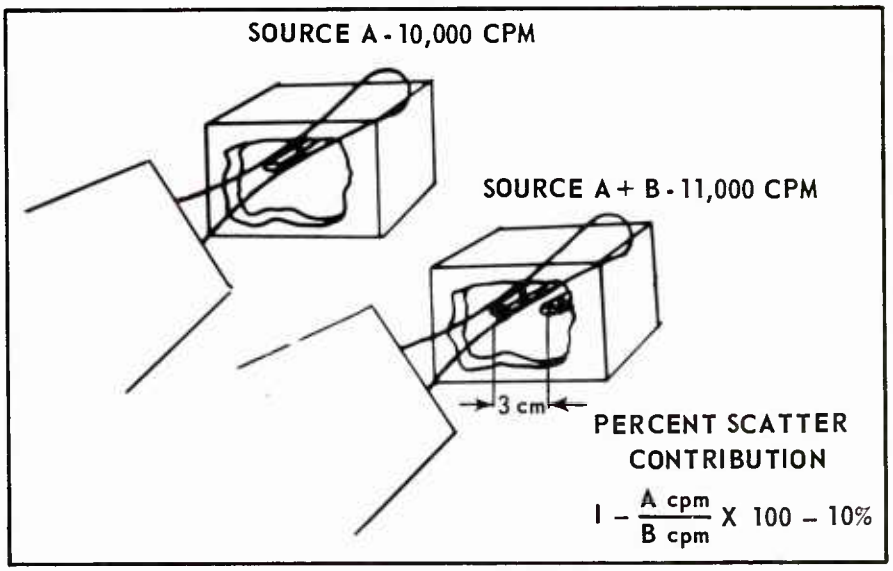

Figure 3. Scatter contribution was assessed in this phantom containing two sources of ^{197}Hg. The degree of overlap was approximately 10 percent when the sources were separated by 2.5 cm.

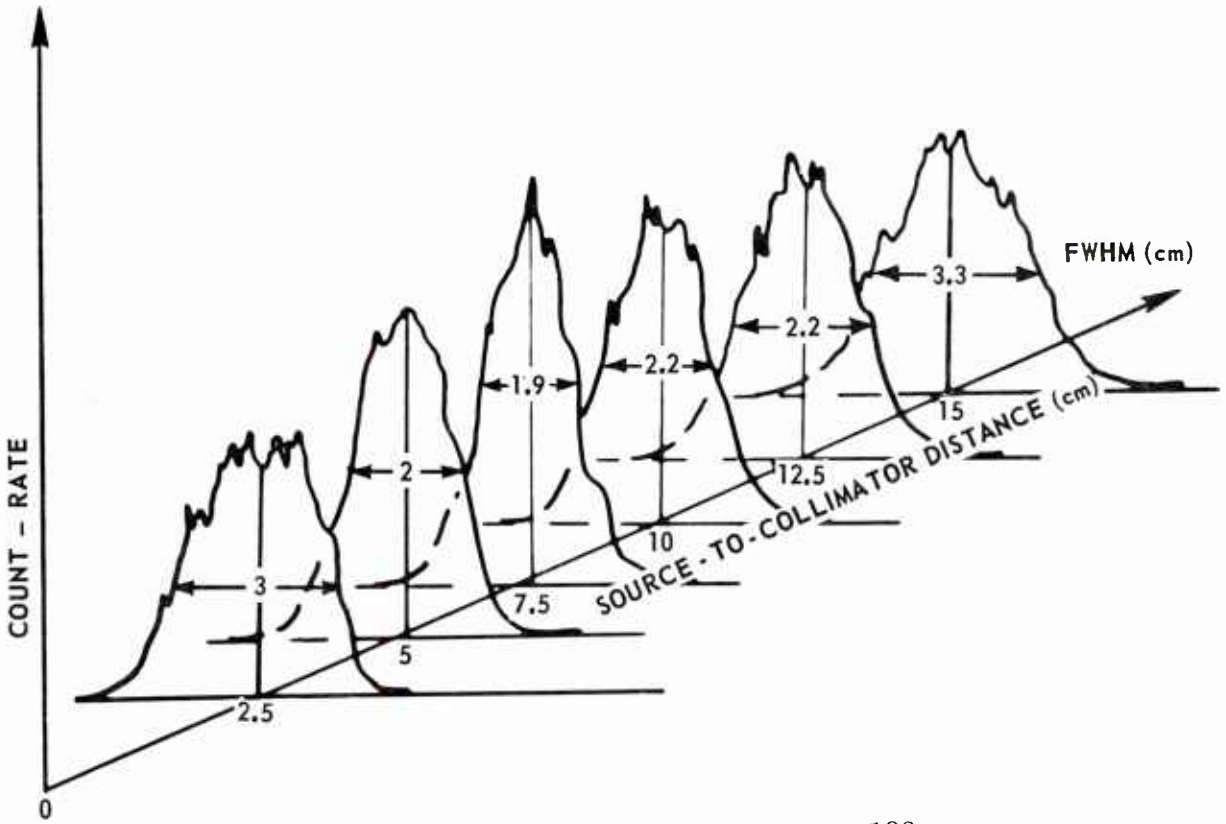

Figure 4. Line spread function studies utilizing ^{133}Xe sources

total activity was recorded. An approximate 10 percent Compton scatter contribution was noted. In addition, isoresponse and line spread function studies (Figure 4) indicated that the response from tissue cores could be completely isolated for center to center separation distances of 3 cm or greater.

In determining the position of the pericallosal probe in the animal, the nasion and inion served as useful reference points (Figure 5). On angiography and at postmortem dissection, the main portion of the pericallosal artery was found to run in a plane 1 cm cephalad and parallel to the nasion-inion line. The pericallosal probe, centered 7 mm above the nasion, detected activity in a core of tissue whose central axis was parallel to the nasion-inion line. The middle cerebral artery probe was centered 7 mm above and 3 mm medial to the lateral canthus of the eye; and its central axis was inclined 30^{o} above the canthomeatal line. As a basis for comparison, conventional CBF_r measurements were made by focusing the same crystal-collimator combination over frontal, temporal and parietal regions.

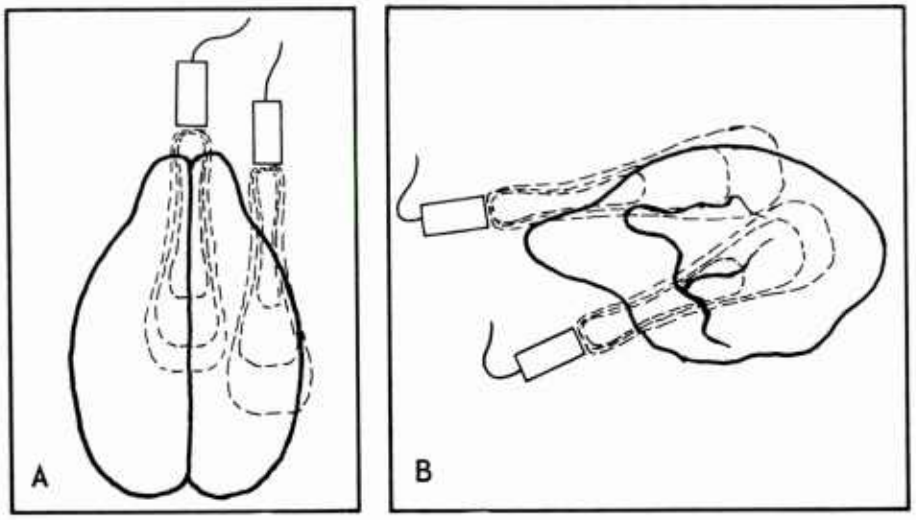

Figure 5. Orientation of focusing collimated probes in (A) vertex view and (B) lateral view to illustrate the position of the pericallosal probe (7 mm above and oriented parallel to the nasion-inion line) and the middle cerebral probe (7 mm above and 3 mm medial to the lateral canthus of the eye and inclined 30^{o} above the canthomeatal line).

The detector output for all studies was subjected to pulse height analysis, using a single channel analyzer with a window width (ΔE) of 21.4 keV. Analyzer printout was obtained from a ratemeter-chart recorder combination (Picker Corporation, White Plains, New York), using a time constant of 1 second and a chart speed of 0.75 inch/minute. The printouts consisted of exponential washout curves containing at least two independent components. These curves were replotted on semilog paper and corrected for background radioactivity. The initial activities (I_1, I_2) of each component were extrapolated to time $t=0$ and then the half time of elimination of each component t1(1/2), t2(1/2) was determined. Both CBF_1 and CBF_r values were then calculated using Lassen et al.'s formula,[10]

$$CBF = 100 \frac{I_1 (0.83) K_1 + 0.73 I_2 (K_1/K_2) 1.57 K_2}{I_1 + 0.73 I_2 (K_1/K_2)}$$

where K_1 and K_2 are the time constants of the fast and slow phases. The average blood flow rates per 100 grams of brain tissue were calculated from these curves using partition coefficients of 0.83 and 1.57 (at mean hematocrit 44 percent) for fast and slow components, respectively.[9,12]

By experimental design, the sequence of measurements was alternated between CBF_r and CBF_1 studies to negate the possibility that differences between them were related to changes in physiological factors such as body temperature, arterial gas concentration, and perfusion pressure.

IV. RESULTS

Sixteen monkeys tolerated the procedures well. Respiratory distress was never observed, and serial determinations of arterial PCO_2 and mean blood pressure during

the 10-minute washout period showed no significant change. Twenty-five CBF_r studies and twenty-seven CBF_l studies were considered technically satisfactory. The washout curves in all experiments demonstrated nonlinear decay, representing the sum of two or more exponentials.

Regional cerebral blood flow. For comparative purposes, CBF_r studies consisted of recordings made over the lateral convexity of the frontal, temporal and parietal regions in 11 animals. Satisfactory decay curves were obtained in 11 frontal, 9 temporal and 5 parietal studies. The average CBF_r value for the frontal region was 40.9 ± 4.9, the temporal 36.1 ± 4.3 and the parietal 37.6 ± 3.4 (Table I). These values are not significantly different.

Table I. Cerebral Blood Flow (cc/100 g per minute)

Animal #	Regional			Local	
	Frontal	Temporal	Parietal	Pericallosal	Middle Cerebral
30	32.9	35.7	37.7	66.0	48.7
31	44.9	32.0	42.0	92.1	54.5
32	35.0	30.0	32.8	-	69.3
33	45.0	39.2	36.4	61.1	52.3
34	38.8	31.5	39.0	63.2	49.5
35	43.8	39.6		65.7	33.7
36	43.2	42.7		69.6	48.0
37	37.2	38.2		36.6	59.5
38	49.5	35.6		68.2	43.7
39	38.6			64.7	51.4
40	41.0			67.4	51.7
41				67.22	44.7
42				67.60	
43				63.3	
44				61.1	
45				74.0	
Average	40.9	36.1	37.6	65.9	50.6
S.D.	4.9	4.3	3.4	11.0	8.7

Local cerebral blood flow. These CBF_1 studies were carried out in 15 animals, 11 of whom had also been studied in the previous group. The pericallosal region consistently displayed a significantly higher ($p < .01$) average flow rate (65.9 ± 11.0) than the region of the middle cerebral artery (50.6 ± 8.7) (Table I). The variability associated with local blood flow measurements was significantly greater ($p < .01$) than the variability of the regional studies. Using the Behrens-Fisher t-test, the difference between the pericallosal values and the regional flow values was very highly significant ($p < .001$). The difference between the middle cerebral studies and the regional studies was highly significant ($p < .01$).

The rapidity with which ^{133}Xe was cleared from both gray and white matter was estimated from the half time of each component of the curve (Table II). The mean middle cerebral t/2 for the fast component was 0.33 minutes while the slow component had a mean t/2 of 3.77 minutes. In the pericallosal area, the mean t/2 for the fast component was 0.34 minutes and 2.83 minutes for the slow component. Triphasic decay curves were recorded from the pericallosal area in eight instances (see Figure 6) and consisted of a third component with a mean t/2 of 5.87 minutes.

Relative weight. To determine the relative weights of fast and slow components of each region, computations based on those of Ingvar et al.[7] were used. The results are displayed in Table II. The fast component accounted for .40 by weight of the tissue recorded from the pericallosal territory, and .42 by weight of the tissue recorded from the middle cerebral territory.

Animal #	Pericallosal*				Middle cerebral*		
	t/2'	t/2''	t/2'''	I_1/I_1+I_2	t/2'	t/2''	I_1/I_1+I_2
30	.16	2.70		0.44	.66	2.60	.48
31	.17	4.70		0.49	.50	2.80	.45
32	-	-	-	-	.30	1.80	.32
33	.17	1.91	6.33	0.46	.33	3.30	.48
34	.42	2.60	6.10	0.59	.25	2.50	.38
35	.33	3.33	5.50	0.26	.25	2.50	.42
36	.25	1.75		0.40	.75	2.50	.40
37	.83	5.42		0.39	.33	1.90	.42
38	.16	2.70	5.75	0.46	.17	6.33	.40
39	.15	2.90	5.88	0.43	.12	6.40	.40
40	.60	2.95	6.00	0.32	.19	5.91	.43
41	.61	2.60	5.44	0.30	.10	6.67	.54
42	.59	2.60	6.00	0.38			
43	.20	2.70		0.43			
44	.33	1.83		0.26			
45	.16	1.75		0.33			
Average	.34	2.83	5.87	0.40	.33	3.77	.42
S.D.	.22	1.34	0.26	.09	.21	1.93	.06

Table II. Compartmental Analysis of Local Cerebral Blood Flow

* t/2', t/2'', t/2''' = half time for washout of first, second and third components

I_1/I_1+I_2 = relative weight of fast component

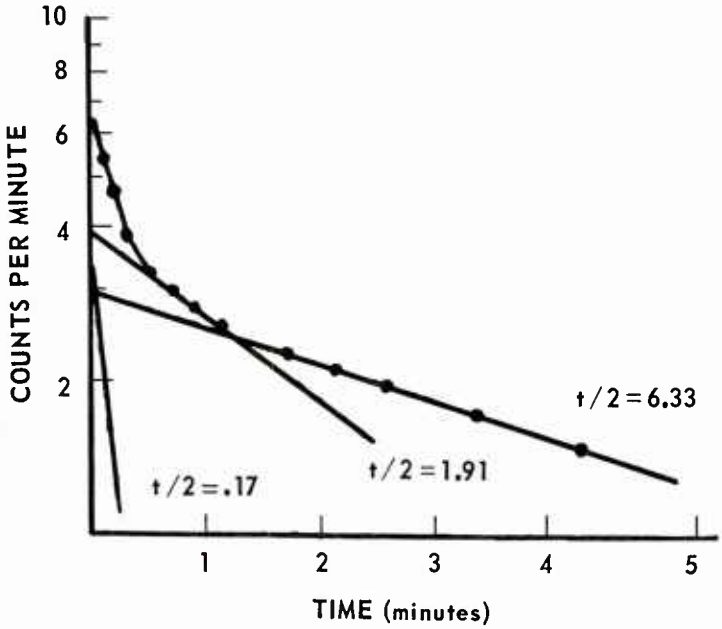

Figure 6. Washout curve from pericallosal region with very fast, intermediate and very slow components. Similar patterns were observed in seven other studies within this territory.

V. DISCUSSION

The intracarotid injection of ^{133}Xe allows simultaneous measurements of the cerebral blood flow in multiple regions of the brain, but conventional methods do not allow one to correlate disease of a particular cerebral artery with flow changes in the territory which it perfuses. By recording from the cerebral convexity with probes oriented laterally, virtually all emissions traveling in a medial to lateral direction are detected. With multiple sources of activity, the counting fields can be represented by truncated cones overlapping more at their medial bases and less at their lateral apices (Figure 1). As a result of Compton scatter, the effect of medial overlapping will be even more marked. Lateral probes will therefore record a large contribution from the deep layers and the inverse square law of distance does not assure a significantly higher counting rate from more superficial than deep layers. Point source measurements and estimates of counting efficiency reported by Ingvar et al.[7] indicate that the inner third of the cerebral hemisphere may contribute up to one-third of the counts seen by a laterally placed convexity probe. By performing isoresponse analyses of two point sources oriented in the sagittal and midsagittal planes to simulate the medial and lateral cerebral hemispheric surfaces, we have noted that this contamination may represent up to 40 percent of the total activity seen by a lateral convexity probe. Therefore, CBF_r measurements are clearly not representative of the flow within specific arterial territories. CBF_r measurements within the parietal lobe may be dependent on the activity carried to it by the middle cerebral artery but the pericallosal-anterior cerebral system undoubtedly contributes to CBF_l, as recorded over the convexity, and it is difficult to correlate specific abnormalities of the major

cerebral arteries with alterations in CBF_r. In studying such circulatory changes, Paulson[11] noted similar problems and concluded that the CBF_r technique was inadequate for measuring changes in flow after middle cerebral occlusion. An attempt to refine the technique of CBF recording was made by Yamamoto et al.[14] who monitored the passage of ^{133}Xe through small areas of cortical infarction created by distal middle cerebral ligation. Their method required exposure of the cortex and identification of the compromised arterial territory with fluorescein angiography.

We have attempted to measure local cerebral blood flow extracranially by reorienting the isotope detectors and utilizing small focusing collimators to record from territories subserved by either the anterior or middle cerebral arteries. The volume of tissue recorded from is essentially a cylindrical core within the distribution of a major cerebral artery. Utilizing this technique, overlap concentration should account for only 10 percent of total activity.

The average CBF_l value obtained for the middle cerebral area was close to that found for the frontal and parietal regions by the more conventional CBF_r method. Clearance times and relative weights of gray and white matter were also comparable. This tends to confirm the notion that the type of tissue which the detector "sees" is, in both cases, of similar consistency.

The higher value for CBF_l measured for the pericallosal area is not readily explicable. The presence of both the large sagittal sinus and a pericallosal artery common to both hemispheres may affect the washout of isotope in a manner similar to that of a large arteriovenous malformation. Although gray-white ratios were similar to those of the middle cerebral territory, the frequent occurrence of triphasic

exponentials contributed a relatively slow component to the average CBF_1 recorded in the pericallosal area.

A definite limitation of the method is the necessity for individual studies of pericallosal and middle cerebral areas since the large collimators restrict the number of probes which can be accommodated in one module. Considering the limitations of presently designed collimators however, this must be accepted since the technique is based on a relatively high degree of discrimination. Future studies will investigate the use of the gamma camera and multichannel analyzer. The 1600-word memory system, good spatial resolution and scatter elimination described by Heiss et al.[5] may provide the necessary discrimination between arterial territories.

Separation of the arterial areas within the posterior circulation seems too formidable with presently available resolution techniques and we have therefore restricted our attempts to a separation of the pericallosal-anterior cerebral area from the middle cerebral area. Studying each area separately requires a crystal-collimator combination whose isoresponse characteristics allow the activity within the region to be detected with minimal overlap from adjacent areas. Our attempts to date have been limited to the rhesus monkey; however, the foregoing considerations will be equally important in clinical applications of the method.

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13. ABSTRACT

An experimental method for determining local cerebral blood flow (CBF_l) within the area of supply of a major cerebral artery is described, using xenon-133. Utilizing anatomic-radiologic correlates, the territories of the anterior and middle cerebral arteries were defined in the rhesus monkey. Highly focused collimation was used so that isoresponse patterns allowed detection of activity from each territory separately. Compton scatter contributed only 10 percent to the total activity seen. CBF_l values were consistently and significantly higher in the anterior than in the middle cerebral distribution. The significance of these findings is discussed.

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